EXTENDED REPORT

Bosentan treatment for pulmonary arterial hypertension related to connective tissue disease: a subgroup analysis of the pivotal clinical trials and their open-label extensions

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Background: Endothelin-1 is considered to be a central pathogenic factor in connective tissue diseases (CTDs) such as systemic sclerosis (SSc), leading to vasoconstriction, fibrosis, hypertrophy and inflammation. A frequent complication of CTD is pulmonary arterial hypertension (PAH), which has a major effect on functioning and quality of life, and is associated with a particularly poor prognosis.
Objective: To present a subgroup analysis that summarises experiences from the pivotal studies and their open-label extensions with the oral dual endothelin-1 receptor antagonist bosentan in patients with PAH and CTD, mostly SSc and lupus erythematosus.
Methods: 66 patients with PAH secondary to CTD, in World Health Organization functional class III or IV, were randomised to two double-blind, placebo-controlled studies and followed up for 12 and 16 weeks, respectively. The primary end point was change in exercise capacity, assessed using the 6-min walk test. In both studies and their extensions, survival was assessed from start of treatment to death or data cut-off and analysed as Kaplan–Meier estimates.
Results: 44 patients with PAH secondary to CTD who were treated with bosentan were stable in 6-min walk distance at the end of the study (+19.5 m, 95% confidence interval (CI) −3.2 to 42.2), whereas patients treated with placebo deteriorated (−2.6 m, 95% CI −54.0 to 48.7). 64 patients subsequently received bosentan in an open-label long-term extension study. Mean (standard deviation (SD)) exposure to bosentan was 1.6 (0.9) years, and duration of observation was 1.8 (0.8) years. 8 (16%) patients received epoprostenol as add-on treatment and 7 (14%) after discontinuation of bosentan. Survival in those receiving bosentan was 85.9% after 1 year and 73.4% after 2 years.
Conclusion: Short-term bosentan treatment in a subgroup of patients with PAH secondary to CTD seems to have a favourable effect compared with placebo. The long-term follow-up of these patients suggests that first-line bosentan, with the subsequent addition of other PAH treatments if required, is safe for long-term treatment and may have a positive effect on outcome.

Pulmonary arterial hypertension (PAH) is a devastating disease of progressive vasculopathy, leading to right heart failure and eventually to death.[1] A considerable proportion of patients with PAH develop the disease secondary to connective tissue disease (CTD). Recent estimates suggest that 10–15% of patients with systemic sclerosis (SSc)[2] and 6–14% of patients with systemic lupus erythematosus [3 4] have PAH. Furthermore, patients with PAH secondary to CTD have a poorer prognosis than people with other forms of the disease.[5] This raises the question of whether the pathological mechanism in PAH secondary to CTD is the same as in other forms of the disease, such as idiopathic PAH, and whether interventions developed for the wider PAH population are effective in the subgroup of patients with PAH secondary to CTD.

Endothelin is a key pathogenic mediator of PAH secondary to CTD. Endothelin drives PAH disease by binding to two receptors, endothelin$_A$ (ET_A) and endothelin$_B$ (ET_B), resulting in deleterious structural changes of the pulmonary vasculature.[6] Bosentan is an oral, dual ET_A/ET_B receptor antagonist, which blocks the effects of endothelin.[7] Bosentan is an approved treatment for PAH and, in two pivotal trials, has shown efficacy in a mixed population, including patients with idiopathic PAH and PAH secondary to CTD.[8 9] However, no in-depth analysis has been conducted of the subset of patients with PAH secondary to CTD, nor has the long-term outcome of these patients been studied and characterised. Thus, this article presents the short-term and long-term outcomes of the PAH secondary to CTD subset of patients from the pivotal studies of bosentan in PAH.

METHODS

Patient population

The patients studied had severe symptomatic PAH at entry, defined as having symptoms on mild exertion or at rest (World Health Organization (WHO) functional class III or IV[10]). Baseline 6-min walk test distance (6MWD) was between 150 and 500 m. Additional entry criteria included mean pulmonary arterial pressure >25 mm Hg, pulmonary vascular resistance >240 dyn s/cm^5 and pulmonary capillary wedge pressure <15 mm Hg as measured by right heart catheterisation. All patients had a confirmed diagnosis of CTD in addition to PAH. Patients with marked interstitial lung disease, determined by forced vital capacity <70% predicted, were excluded from the studies. They had no

Abbreviations: CTD, connective tissue disease; 6MWD, 6-min walk test distance; PAH, pulmonary arterial hypertension; SSc, systemic sclerosis; WHO, World Health Organization

previous exposure to prostanoids and conventional treatment was based on the discretion of the treating doctor.

Randomised, double-blind, placebo-controlled trial design

Patients were randomised to receive placebo or bosentan in one of the two pivotal studies: study 351 or Bosentan: Randomised Trial of Endothelin Receptor antagonist Therapy for Pulmonary Arterial Hypertension (BREATHE-1). Those randomised to bosentan received an initial dose of 62.5 mg twice daily for 4 weeks, before up-titration to the target dose (125 or 250 mg twice daily) for a further 8 or 12 weeks; a total of 12 or 16 weeks' duration of study drugs. Any patients requiring prostanoid treatment during the course of the study were withdrawn. At the end of the treatment period, efficacy was assessed by 6MWD, WHO functional class and time to clinical worsening. Patients who completed the placebo-controlled study were eligible to participate in the open-label extension study.

Open-label extension trial design

All patients recruited to the open-label extension trials received bosentan 62.5 mg twice daily for 4 weeks before up-titration to the target dose of 125 mg twice daily, irrespective of whether they had received bosentan or placebo during the randomised phase, as the study was still blinded. Subsequent up-titration to 250 mg twice daily was allowed in cases of clinical deterioration. During the extension studies, parenteral prostanoid or other treatments could be added to bosentan treatment if clinically indicated.

Patient outcome data recorded included bosentan initiation and stopping dates, date of last visit, status at the date the patient was last seen (alive/dead, without documentation of reason for death), the date of lung transplantation and the date of initiation of prostanoid treatment. Data on survival status and alternative treatments were collected from the start of the first placebo-controlled study to data cut-off, whether or not patients remained on study treatment throughout.

Good clinical practice

All studies were conducted in accordance with the amended Declaration of Helsinki at sites in North America, Europe, Australia and Israel. The local ethics review committees approved the protocols, and written informed consent was obtained from all patients.

Statistical analyses

Patient data from study 351 or BREATHE-1 were pooled, as the study designs were almost identical. Descriptive statistics were appropriate as this was not a predefined patient group to be analysed. Baseline and follow-up information were summarised as mean (standard deviation (SD)) or frequency counts and proportions. Baseline parameters were recorded at the start of bosentan treatment where possible. Missing values in the analysis of the randomised, double-blind, placebo-controlled trials were derived by using predefined replacement rules to minimise bias. For patients who discontinued the study drugs because of clinical worsening, the values recorded at the time of discontinuation were used; patients for whom no value was recorded (including those who died) were assigned the worst possible value (0 m). For all other patients without a week 12 or 16 assessment, the last 6MWD and WHO functional class were used as week 12 or 16 values, respectively.

Clinical worsening was defined as the combined end point of death, lung transplantation, hospitalisation for pulmonary hypertension, lack of clinical improvement or PAH worsening leading to discontinuation, need for epoprostenol treatment or atrial septostomy. Time to clinical worsening was defined as the time elapsed from the start of study treatment to the first occurrence of an event indicating clinical worsening. Patients without the event were censored at the end of the treatment period (ie, at the day after the last day of study drug intake).

Exposure to bosentan was calculated from the start of active treatment, either the start of the randomised study (for patients randomised to bosentan) or the start of the extension study (for patients randomised to placebo).

Survival was assessed from the start of treatment to death or data cut-off. Kaplan–Meier estimates for up to 24 months were reported with 95% confidence intervals (CI). Vital status and treatment at 12 and 24 months were summarised as the proportions of patients who entered the 12-month and 24-month periods, respectively. Patients who had been followed up for <12 month were not included in the 24-months summary.

In the summary of adverse events, only treatment-emergent events were considered and coded according to the MEDRA 3.3 dictionary.

RESULTS

Randomised, double-blind, placebo-controlled phase

In all, 66 patients with PAH secondary to CTD were randomised to participate in the pivotal studies; 44 of these patients received bosentan and the remaining 22 received placebo. All bosentan-treated patients with PAH secondary to CTD were included in the analyses (intent to treat); there were no patients lost to follow-up (fig 1).

Baseline characteristics

Table 1 shows the baseline demographics of patients with PAH secondary to CTD in the bosentan and placebo groups. The bosentan group had a higher proportion of women than men (86.4% *v* 77.3%, p = not significant (NS)), the patients were older (mean age 57.7 *v* 49.7 years, p = 0.02) and had a higher proportion of patients with PAH secondary to SSc than in other PAH secondary to CTD aetiologies (84.1% *v* 68.2%, p = NS). Baseline disease characteristics showed similar proportions of patients in WHO functional classes, with 95.5% of patients in both groups being in WHO functional class III at baseline, and all remaining patients in class IV. However, there were differences in haemodynamic characteristics suggesting more severe disease in the bosentan group at baseline, in particular the 6MWD (312 *v* 361 m, p = 0.01) and pulmonary vascular resistance (809 *v* 722 dyn s/cm^5).

6-min walk test

Exercise capacity, measured by the 6-min walk test, remained stable at the end of the study (week 12 or 16) in the 44 patients with PAH secondary to CTD treated with bosentan (primary end point, +19.5 m, 95% CI −3.2 to 42.2). The exercise capacity of 22 patients with PAH secondary to CTD who were treated with placebo deteriorated by −2.6 m (95% CI −54.0 to 48.7), leading to a trend in favour of bosentan, an absolute difference of 22.1 m (95% CI −32 to 76, p = NS).

Time to clinical worsening

Time to clinical worsening was delayed by bosentan at the end of the first treatment period, suggesting slower disease progression. The Kaplan–Meier estimates of the percentage of event-free patients showed trends of slower disease progression for bosentan versus placebo: 95.4% for bosentan and 90.9% for placebo at 12 weeks; 90.3% for bosentan and 86.4% for placebo at 16 weeks (fig 2).

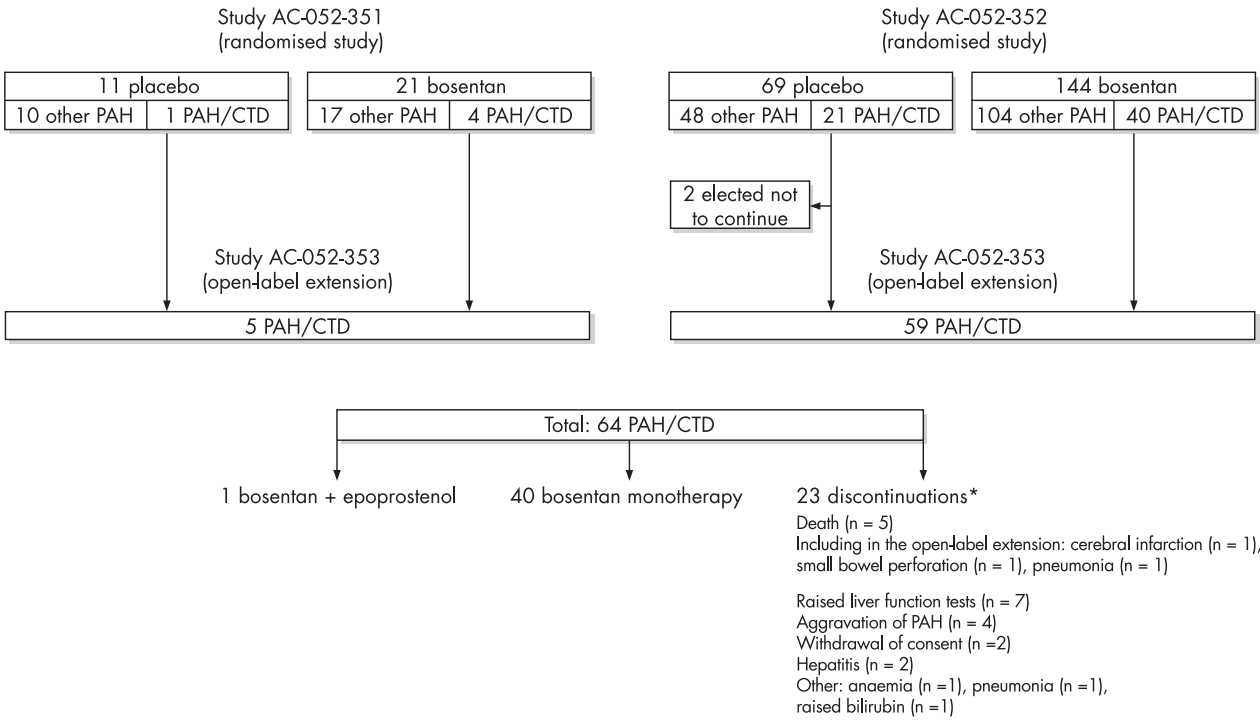

Figure 1 Patient disposition in the two pivotal studies and their long-term extensions. AC-052-35 (study 351; AC-052-352, Bosentan: Randomised Trial of Endothelin Receptor antagonist Therapy for Pulmonary Arterial Hypertension (BREATHE-1); CTD, connective tissue disease; PAH, pulmonary arterial hypertension. *, Patient numbers include four patients discontinued during the double-blind phase of BREATHE-1, which is part of the survival analysis.

Adverse events

The most frequent adverse events in the bosentan group versus placebo group were dizziness (18.2% *v* 4.5%), lower limb oedema (18.2% *v* 4.5%), headache (15.9% *v* 22.7%) and fatigue (13.6% *v* 0%). Abnormal hepatic function occurred in 11.4% of patients treated with bosentan versus 9.1% of patients treated with placebo. These differences between incidences were not significant on statistical testing.

Table 1 Demographic and clinical baseline characteristics of patients with PAH secondary to CTD at the beginning of the randomised studies

	Bosentan-treated patients (n = 44)	Placebo-treated patients (n = 22)
Sex (men/women), n (%)	6/38 (13.6/86.4)	5/17 (22.7/77.3)
Age (years)		
Mean (SD)	57.7 (12.6)	49.7 (12.7)
Range	33.0–80.0	18.0–67.0
Race, n (%)		
Caucasian	36 (81.8)	19 (86.4)
Black	7 (15.9)	1 (4.5)
Other	1 (2.3)	2 (9.1)
Time from diagnosis (days)		
Mean (SD)	791 (967)	475 (716)
Aetiology of PAH, n (%)		
PAH/SSc	37 (84.1)	15 (68.2)
SLE	5 (11.4)	3 (13.6)
Overlap syndrome	1 (2.3)	3 (13.6)
CTD (unclassified)	1 (2.3)	1 (4.5)
WHO functional class, n (%)		
III	42 (95.5)	21 (95.5)
IV	2 (4.5)	1 (4.5)
Cardiac haemodynamics (mean (SD))		
CI (l/min/m^2)	2.4 (0.8)	2.5 (0.8)
PVR (dyn s/cm^5)	809 (451)	722 (365)
mPAP (mm Hg)	47 (12)	45.1 (10.6)
mRAP (mm Hg)	8.4 (5.1)	8.0 (5.0)
PCWP (mm Hg)	8.9 (3.4)	9.9 (5.1)
6-min walking distance (m)		
Mean (SD)	312 (73)	361 (67)

CI, cardiac index; CTD, connective tissue disease; mPAP, mean pulmonary arterial pressure; mRAP, mean right arterial pressure; PAH, pulmonary arterial hypertension; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; WHO, World Health Organization.
Data are taken from studies 351 and BREATHE-1. Results of the full dataset have been published in Channick *et al*[8] and Rubin *et al*.[9]

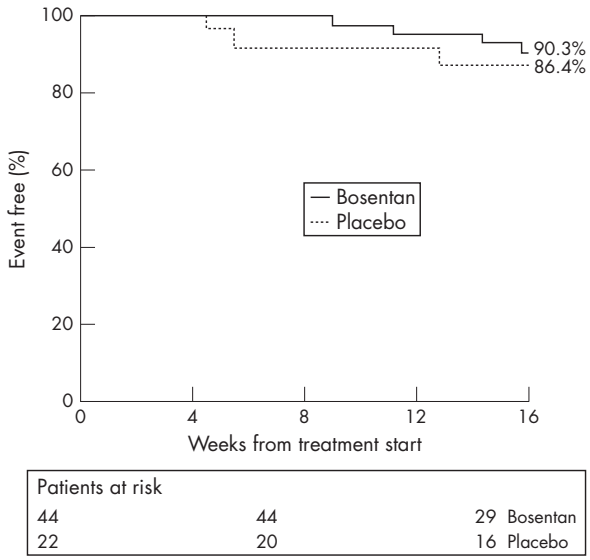

Figure 2 The Kaplan–Meier estimates display the time to clinical worsening in patients with pulmonary arterial hypertension (PAH)/ connective tissue disease (CTD) treated with bosentan or placebo in the two pivotal studies. Time to clinical worsening is the combined end point of death, lung transplantation, hospitalisation for pulmonary hypertension, lack of clinical improvement or PAH worsening leading to discontinuation, need for epoprostenol treatment or atrial septostomy. ''Patients at risk'' exclude those patients for whom data at the specified time point was not available, or censored patients. One placebo patient was in study 351 and hence received open-label bosentan from week 12 onwards in the extension study.

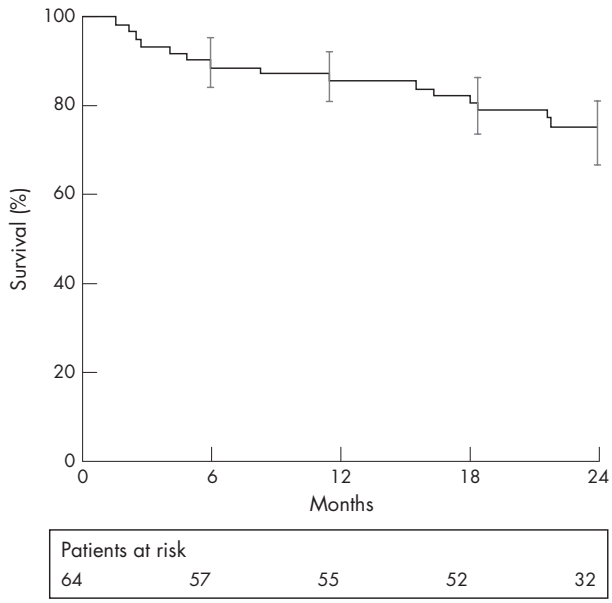

Figure 3 The Kaplan–Meier estimates display the observed survival of the 64 patients with pulmonary arterial hypertension (PAH) secondary to connective tissue disease (CTD) who were included in the two double-blind studies and followed up in the open-label study extensions. Survival on bosentan was 85.9% after 1 year and 73.4% after 2 years. Patients are considered from the double-blind, randomised studies 351 and BREATHE-1 and their open-label follow-up studies. Kaplan–Meier survival estimates with 95% confidence limits for patients with PAH related to CTD, given bosentan as the preferred treatment. As the number of patients was decreasing over time, the cut-off date was chosen as month 24.

Long-term extension phase

Of the 66 patients in the double-blind studies, two patients treated with placebo elected not to enter the long-term extension phase, and 64 continued into the open-label extension studies (fig 1). Of these, 40 remained on bosentan monotherapy, 1 received prostanoids in addition to bosentan and 19 discontinued during the follow-up period. Together with 4 discontinuations of patients with PAH secondary to CTD during the double-blind phase of the BREATHE-1 study, a total of 23 discontinuations were recorded (reasons provided in fig 1). The mean duration of observation for all patients was 1.8 (SD 0.8) years (range 0.1–3.2). It was similar to the mean time on bosentan (1.6 (SD 0.9); range 0.1–3.2), which allows a reasonable assessment of vital status while receiving bosentan treatment. During the observational period, 8 (16%) patients received intravenous epoprostenol as add-on treatment and 7 (14%) patients received it after discontinuation of bosentan.

WHO functional class and 6MWD

Of the 40 patients on bosentan monotherapy, 25% improved in WHO functional class by the end of treatment (23% of ex-bosentan patients and 29% of ex-placebo patients). 6MWD in patients on monotherapy increased from mean 352 (SD 94) m by +14.7 (80) m (95% CI −11 to 40).

Survival

At data cut-off, vital status was known for all patients in the database. The Kaplan–Meier estimates for the observed survival are presented in fig 3. Survival was 85.9% at 1 year and 73.4% at 2 years (patient numbers at 3 years were too low to calculate a robust estimate).

DISCUSSION

Various systemic rheumatic diseases or CTD are associated with PAH, including SSc both in the diffuse and limited forms, systemic lupus erythematosus, overlap syndromes and rheumatoid arthritis.[2 4 11] Irrespective of its aetiology, PAH is characterised by changes in the small pulmonary arterioles, including intimal fibrosis, medial hypertrophy, adventitial proliferation, in situ thrombosis, fibrinoid necrosis and plexiform lesions, all leading to a progressive increase in pulmonary vascular resistance.[12] The consequence of this is pulmonary hypertension leading to right ventricular failure with high mortality.[2 5 13 14]

With the availability of epoprostenol and bosentan as licensed treatments for PAH, including PAH secondary to CTD, treatment options for this population have improved considerably. However, it is difficult to quantify the net effect of the new treatment options, as it is no longer ethically justifiable to perform placebo-controlled trials in patients with PAH in WHO class III and IV. Hence, the present subgroup analysis represents an important source of data on the effect of bosentan in PAH secondary to CTD.

The randomised double-blind, placebo-controlled phase showed a trend towards a mean treatment effect in patients with PAH secondary to CTD in the 6-min walk test, which can be interpreted as stabilisation of disease. It is important to consider not only the relatively short-term outcome measures such as exercise capacity in these patients but also the long-term effect of treatment. To assess this, all patients were followed up from the start date of bosentan treatment until their death or the cut-off date. As none were lost to follow-up, this provides a comprehensive and credible database. The long-term data show that for patients with severe PAH secondary to CTD, the 1-year survival on bosentan was 86% and the 2-year survival was 73%. These survival rates were considerably higher than those of a historical cohort of untreated patients with PAH secondary to CTD reported by Koh *et al*[13] (1-year and 2-year survival only at

approximately 45% and 35%, respectively). Advances in the general management of patients with PAH have probably improved patient outcomes compared with these historical data. The long-term outcomes on bosentan are at least comparable to the recently published survival data from 45 patients with PAH associated with scleroderma in the Royal Free Hospital registry.[15] In these patients receiving bosentan-based monotherapy and combination therapy, survival was 81% and 71% at 1 and 2 years from PAH diagnosis, respectively. Outcomes compared favourably to the 68% and 47% 1-year and 2-year survival of a historical cohort of 47 patients in the same institution who had been treated (before bosentan was available) with conventional treatment, including prostanoids (n = 27). Patients enrolled in a clinical trial are likely to be different and indeed baseline values of patients in our study were different from those in the registry. However, it gives an indication of the expected outcomes in clinical practice and so is a relevant comparison for clinicians.

The long-term findings in our study have to be interpreted against the background of potential limitations. The number of patients in this retrospective analysis was low. We also observed some differences in the baseline disease characteristics between the two cohorts—for example, higher age, longer PAH evolution and shorter 6MWD in the bosentan group. The longer PAH evolution and shorter 6MWD suggest more severe disease in the bosentan group, which might have biased the magnitude of treatment effect. In addition, after the end of the placebo-controlled part of the study patients were able to receive additional treatments for PAH as well as bosentan, which might have contributed to the treatment effect.

Although these limitations must be considered, they also mean that our outcome data are likely to be representative of current practice to the treatment of PAH secondary to CTD fulfilling the entry criteria for these trials at baseline.

CONCLUSION

The short-term, placebo-controlled phase of this analysis shows the potential utility of blocking endothelin with bosentan in this subset of patients with PAH related to CTD. These patients have previously been shown to have a particularly poor prognosis. This analysis suggests that first-line bosentan, with the subsequent addition of other PAH treatments, if required, is safe for long-term treatment use and may have a positive effect on outcome. Further studies are warranted.

DISCLOSURES

The authors have received research funding from and have participated on the advisory boards of clinical trials. They have been consultants to Actelion Pharmaceuticals, the manufacturer of bosentan. All authors of this study have received research funding from, acted as advisors to, or served on trial steering committees for Actelion Pharmaceuticals.

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Competing interests: None declared.

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